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THE HEALTH EFFECTS OF LOW LEVEL EXPOSURE TO LEAD[1]

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INTRODUCTION

The uses of lead and its toxic properties at high dose have been recognized since antiquity (1). Recent research has concentrated on the subclinical toxicity of lead, that is, on the question of whether unrecognized health effects are produced by lead at doses well below those which yield unequivocal clinical symptoms. Despite often intense controversy, a great volume of work in the past decade has demonstrated that lead produces a dose-related continuum of toxicity that ranges from enzymatic inhibition in red blood cells, through slowing of nerve conduction velocity, to colic, wrist drop, and encephalopathy. Although knowledge of the low-dose effects of lead is still incomplete, the direction and consistency of the available data have been sufficiently convincing to governmental agencies in the United States that they have issued a series of standards and recommendations intended to protect the health of the public by reducing exposure to lead from a number of sources. These standards have frequently incorporated margin-of-safety calculations that are intended to protect against additional, yet unrecognized, sequelae of low-dose, long-term lead exposure. Among these standards (Table 1) are the Center for Disease Control's (CDC) recommendations on preventing lead poisoning in young children, the Occupational Safety and Health Administration's (OSHA) standard for

occupational lead exposure, the Consumer Product Safety Commission's (CPSC) standard for lead in household paint, and the Environmental Protection Agency's (EPA) standards for lead in air and in drinking water. Two of these standards (CDC, OSHA) have been recently revised downward as additional information has become available on low-dose lead toxicity.

HISTORY OF LEAD USE

Because lead resists corrosion, tools easily, insulates well, and when compounded makes good pigments, it has been widely used since at least 3500 B.C. (1). Egyptian manuscripts dating back to before the Hebrew Exodus describe the use of lead in ornaments, cosmetics, figurines, and fishing weights. Lead is often found in silver ore, and the Old Testament provides instructions for cupellation—the separation of lead from silver. The Greeks were aware of lead's toxicity. Nikander, a poet and physician of the second century B.C., vividly described the hazards of lead. Pliny warned of the dangers of breathing lead vapors, but it is curious that he advised that wine and grape syrup be stored in lead, rather than copper, vats. The Romans employed lead widely in building and in water conveying. (The word "plumber" derives from the Latin *plumbum:* "lead.") Gilfillan (2) has suggested that the declining birth rate and apparent increased incidence of psychosis in Rome's ruling class, which may have been at the root of the Empire's dissolution, were a result of exposure to lead in food and wine.

The Massachusetts colony in the eighteenth century distilled rum for export to North Carolina. Consumers there were frequently afflicted with "dry bellyache." When lead in the rum was identified as the cause, one of

Table 1 Lead standards and recommendations of United States government agencies

Agency	Year of issue	Material covered	Standard level
Center for Disease Control (CDC)	1970	Blood lead (children)	40 μg/dl whole blood[a]
	1975	Blood lead (children)	30 μg/dl whole blood
Occupational Safety and Health Administration (OSHA)	1971	Air (workplace)	200 $\mu g/m^3$ air[a]
	1978	Air (workplace)	50 $\mu g/m^3$ air
Consumer Product Safety Commission (CPSC)	1976	Household paint	0.06% paint dry wt.
Environmental Protection Agency (EPA)	1978	Ambient air	1.5 $\mu g/m^3$ air
	1980	Drinking water	50 μg/l

[a] Standard revised downward in light of newer toxicologic data.

the first public health acts in America was promulgated (3). This legislation, which banned the use of lead in stills, appears to have been passed more to protect the rum industry than the consumers. At about the same time in England, Sir George Baker established that the epidemic Devonshire colic was caused by lead introduced into cider by apple presses (3).

Important contributions to modern knowledge of lead's toxicity have been made by Alice Hamilton (4), J. L. Gibson (5), and Joseph Aub (6). Byers & Lord (7) first showed that lead intoxication in children left permanent neurological sequelae and suggested that a considerable portion of school children with behavioral difficulties might have undiagnosed plumbism.

SOURCES OF LEAD

Lead enters the biosphere through natural (nontechnological) means from the erosion of soil in lead-bearing rocks. This natural contribution accounts for only an extremely small portion of ambient levels. Patterson has estimated that natural airborne lead levels would be 0.0004 to 0.0012 $\mu g/m^3$ (8). In remote areas air lead levels of 0.009 to 0.019 $\mu g/m^3$ have in fact been measured (9). In contrast, urban air lead concentrations from 1.0 to 3.0 $\mu g/m^3$ are not rare. The increasing use of lead over the past two millenia and the resultant contamination of the biosphere have been accurately estimated by examining the lead content of stable ice field cores. Annual ice layers from the interior of Greenland show steadily increasing concentrations of lead; in addition, there have been sharp upward deviations related in time to the late middle ages, to the industrial revolution (A.D. 1750), and to the proliferation of the automobile (1965). In contrast, ice cores from Antarctica show a much smaller gradient over time (10). The concentration of lead in marine water from the preindustrial era has been estimated to have been 0.02 to 0.04 $\mu g/kg$. While deep samples of contemporary water contain lead at that concentration, surface waters now have lead at concentrations of 0.2 to 0.35 $\mu g/kg$.

ENVIRONMENTAL PATHWAYS

Inorganic lead enters the body through the gut and the respiratory tract. Alkyl lead may be absorbed directly through the skin (10). The major sources of alimentary absorbtion are food, dust, water, and paint. For children the most common high dose source of lead is paint. Household paint applied before the 1940s could contain as much as 50% lead by dry weight. While most children mouth foreign substances, some persist in the habit and may ingest enormous amounts of lead in this fashion. The Lead

Paint Poisoning Prevention Act (1973) set the allowable content of household paint at 0.06% (Table 1). Many households, however, still have painted surfaces that were applied earlier than 1973, and some individuals inadvertently use industrial paint in homes.

Lead enters the food supply through deposition of automobile and industrial emissions on grains and vegetables, through lead-containing insecticides, through animals foraging leaded feeds, and through canning. Canned foods, e.g. evaporated milk, may contain much higher lead concentrations than fresh products. Individual intake of lead through foodstuffs is estimated at 100 to 150 μg per day (11).

Most standing water supplies have low concentrations of lead (12). However, in circumstances where the water is acidic and has low mineral content, lead can be leached from pipes, solder joints, and storage tanks. The current EPA standard for lead in drinking water is 50 μg/l (Table 1).

Airborne lead derives mainly from two sources: stationary sources such as smelters, and automobile emissions. Smelters account for only a small fraction of total airborne emissions, but they can emit large amounts of lead from their stacks and through fugitive emissions and can produce intense local accumulations of lead. This localized environmental contamination can be reflected in elevated blood lead levels in nearby residents (13, 14). Automotive lead emissions from the combustion of alkyl lead in gasoline have been slightly reduced since the introduction in 1975 of catalytic converters; the converters require lead-free fuel. However, in 1975, 189,000 metric tons of lead were used in the manufacture of gasoline antiknock additives in the United States; approximately 75% of that lead was emitted into the air, and automotive emissions remain the major source of lead in ambient air. Lead of small particle size (less than 1 μM) is retained in the lung, and approximately 40% is absorbed. Larger particles are washed out of the larger bronchi, but may then be swallowed. Some airborne lead falls out as dust and then becomes accessible to human ingestion.

Other less common sources of lead are ceramic kitchenware, putty, newsprint, and wines.

PHYSIOLOGY

About 10% of the lead ingested by adults is absorbed from the gut (15). For children the fraction absorbed is considerably higher, perhaps as great as 40% (16). Most lead in the blood is found within the erythrocytes (17). Plasma levels are fairly stable at approximately 3 μg/dl (18). Lead is taken up by most soft tissues, including the brain. The largest storage site is in bone. Rabinowitz and colleagues, using nonradioactive isotopes, have shown that lead is held in three storage pools: (*a*) a fast pool, primarily

blood, with a half-life of about 27 days; (*b*) a slightly slower pool, mainly soft tissue with a half-life of 30 days; and (*c*) a long-term storage pool, primarily bone, with a half-life of 10,000 days (19).

Most lead is excreted in the urine and feces. A smaller amount is lost through hair and fingernails and through skin desquamation. In adults about 90% of ingested lead is found in the feces. It is likely that some portion of the fecal lead has been absorbed and is then secreted in the bile. Lead absorption is enhanced by protein deficiency in the diet, as well as by diminished calcium and iron intake (20). Increased absorption of lead in the presence of dietary fat has also been demonstrated (21).

Factors Affecting Vulnerability of Individuals

The toxic properties of lead are exacerbated by iron deficiency and malnutrition (20). This exacerbation is of importance to public health because the highest exposure to lead is experienced by the urban poor, the same segment of the population at highest risk for undernutrition. Glucose-6-phosphate dehydrogenase deficiency, a frequent finding in blacks, also has been reported to increase susceptibility to lead (22). Roels and colleagues have studied the differential vulnerability of men, women, and children to lead as demonstrated by the shape of the dose-effect curves between lead and aminolevulinic acid dehydrase (ALA-D) activity and between lead and free erythrocyte protoporphyrin (FEP) concentrations. Women were found to be more sensitive than men to lead in terms of their ALA-D and FEP responses. Children were found to be still more sensitive (23).

In general, younger organisms appear to be more sensitive than adults to lead. This heightened susceptibility has been shown for tadpoles (24), rodents (25), and nonhuman primates (26), as well as for children.

Biochemical Toxicology

The study of the biochemical mechanisms that underlie the toxicity of lead (and of other trace metals) is a relatively new field. Lead is a reactive element and combines readily with sulfhydryl groups, phosphates, and other ligands. Because of its affinity for sulfhydryl groups, lead changes the configuration of many enzymes, and generally decreases their activity. Enzymes in which the effects of lead have best been studied are those in the heme pathway (27), the mixed function oxidases (28), and adenylcyclase (29). Recent evidence suggests that lead may inhibit enzymes involved in the activation of vitamin D (30).

The synthesis of heme begins and ends with the mitochondrion (Figure 1). Lead inactivates δ-aminolevulinic acid dehydratase (ALA-D) at extremely low concentrations. Hernberg demonstrated that the log ALA-D concentration is inversely correlated with lead at concentrations as low as

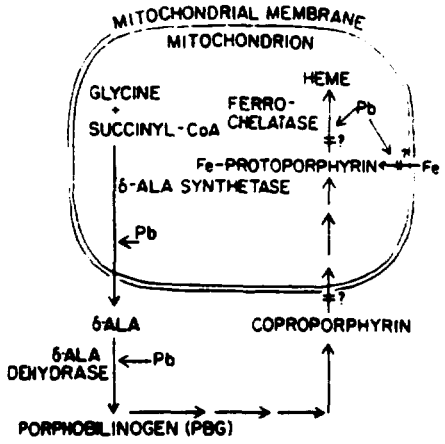

Figure 1 The sites of lead's actions on the heme biosynthetic pathway: 1. δ-ala synthetase activity is increased by lead, either directly or by derepression; 2. δ-ala dehydrase is inhibited; 3. heme formation is decreased by two possible actions, inhibition of ferrochelatase, and inhibition of substrate passage through the mitochondrial membrane.

5 μg/dl (31). In adults, aminolevulinic acid (ALA) begins to increase in the urine when blood lead levels reach 40 μg/dl. The inhibition of ALA-D in blood is paralleled by similar inhibitions in other tissues, including brain (32). δ-Aminolevulinic acid, which accumulates in the presence of lead, has neuroactive properties. It may act as a GABA-agonist on presynaptic receptors and by feedback inhibition may reduce the amount of GABA available at the synapses (35). ALA crosses the blood-brain barrier and is readily taken up by brain tissue (36). In the brain, ALA may inhibit Na and K ATPase (37). ALA uptake in the brain has been shown to produce increased motor activity in rats and gerbils (38) and altered social behavior in mice (39). Increased brain ALA is suggested as a possible mechanism for the disordered behavior and thinking exhibited in cases of porphyria (40) and may be an effect of acute lead intoxication as well.

Decreased brain ALA-D activity in response to increased blood lead levels has been demonstrated (32). Bull et al (41) have shown delays in the development of brain cytochromes in the immature rat at low blood lead concentrations. These changes were accompanied by decreased density of synapses and increased oxygen uptake in response to potassium stimulation (42).

Lead possesses affinity for the mitochondrial membrane and alters the activity of ferrochelatase. Iron uptake by the red cell is diminished in the presence of lead, and heme synthesis is suppressed. Zinc replaces iron, and zinc protoporphyrin then accumulates. Increased levels of either zinc protoporphyrin (ZPP) (33) or its equivalent, free erythrocyte protoporphyrin (FEP) (34), are an early marker of impaired tissue function.

Lead also inhibits the activity of cytochrome P450, and thereby interferes with the mixed function oxidase system (28). This alteration has been shown to prolong antipyrine clearance time (28).

Lead affects adenylcyclase activity at low concentrations in preparations of cerebellar cells (29) and in the striatum (43). Because postsynaptic catecholamine receptors are associated with adenylcyclase activity, the effects of lead micropipeted into the cerebellium of rats were studied by Taylor et al (44). They found that lead blocked norepinephrine inhibition of Purkinje cells.

Lead has been demonstrated to interfere with the synthesis of collagen (45). This effect may be implicated in the capillary fragility of lead encephalopathy. The enzyme 5-pyrimidine nucleotidase, an RNA-scavenging enzyme, is inhibited by lead at low concentration (46). This inhibition is responsible for the basophilic stippling observed in about 50% of clinical cases of lead poisoning.

Children with elevated blood lead levels have been shown to have diminished serum levels of 1,25-dihydroxyvitamin D, the active form of the vitamin, as compared to age-, sex-, and race-matched controls (30). This effect appears to be caused by a dose-related enzymatic impairment of the production of the active hormone in the kidney. Possible consequences of this enzymatic inhibition appear to be slowed bone growth and secondary hyperparathyroidism.

HIGH-DOSE EFFECTS OF LEAD

Lead affects many organ systems at high dose, including the kidney, liver, gut, myocardium, the immune system, the peripheral and central nervous system, and the erythron. At high dose acute abdominal colic may occur, and lead colic has been confused with other acute abdominal conditions requiring surgery. Other early symptoms of high-dose lead absorption are anorexia, myalgia, constipation, irritability, and lethargy. Those symptoms may progress to coma, convulsions, and death. Chronic nephropathy, with tubular degeneration and vascular and glomerular changes, has been described in industrially exposed adults. Wedeen et al (47), employing kidney biopsies in a small series of industrially exposed workers, have shown that tubular damage may occur earlier and at lower dose levels than previously described.

Neurological effects in adults exposed to high lead levels are more likely to be evident in the peripheral nerves, while children usually display central nervous system signs. The peripheral effects are usually reported as limited to the motor nerves producing extensor muscle weakness (foot and wrist drop); however, sensory deficits have also been observed (55). Increased plasma lead levels have been reported in patients with amyotrophic lateral

sclerosis (48). The acute central nervous system changes caused by severe lead exposure in children are due to brain edema and hemorrhage. These events generally occur in children when the blood lead level exceeds 80 μg/dl, but encephalopathy has been reported at lower concentrations (49). A high percentage of children who recover from lead encephalopathy show enduring neuropsychological defects (50). Byers & Lord (7) evaluated 20 children who recovered from lead intoxication, half of whom did not have encephalopathy. Nineteen were found to have behavioral and educational difficulties and impaired perceptual-motor function. The commonly reported sequelae of high dose lead toxicity in children are intellectual deficit (50); attentional disturbance, often with hyperactive behavior (7); and perceptual motor deficiencies (51). Because the symptoms of lead encephalopathy are nonspecific and because many children have blood lead levels greater than 40 μg/dl, considerable recent interest has developed concerning the possible neurotoxicity of lead at lesser does (51–60).

POPULATION STUDIES OF CHILDREN AT LOW DOSE

Because children are more susceptible than adults to lead and because the child's developing brain may be the organ most sensitive to lead, a number of population studies of children exposed to a wide range of lead concentrations have been published since 1972. Considerable variation in both method and conclusions is found in these reports. We attempt to review critically the more salient studies and to examine the issues of design and execution that affect their interpretation.

These reports provide a useful demonstration of some of the difficulties encountered in population studies of lead (or of other neurobehavioral toxicants). The main pitfalls in method or design can be subsumed under the following five categories:

1. Difficulties in accurately classifying exposure: Blood lead is an indirect marker of lead exposure, and while it may accurately index recent exposure, it may return to baseline once exposure stops, even in the presence of an elevated body lead burden. Conversely, blood lead levels may be transiently elevated following brief exposure in otherwise unexposed persons. Misclassification of subjects is therefore a common problem if a single blood lead determination or if proxy variables such as closeness to a pollution source are employed as exposure markers. Such misclassifications can produce either false negative or false positive results, depending upon whether persons with excessive previous lead exposure are mistakenly treated as controls or whether those with brief but recent exposure are mistakenly classified as highly exposed.

2. Ascertainment bias: Persons who participate in a study may differ in some relevant fashion from those who decline the invitation or who are not reached. Parents who suspect that their child has a neurologic deficit may either seek or avoid a given study, depending on how they perceive it. Studies that draw their sample from special clinics or from schools for the developmentally handicapped cannot be employed to draw generalizations to larger communities. In general, population-based studies with high participation rates provide the most reliable, bias-free data. Errors in ascertainment can lead to either false positive or false negative conclusions.

3. Lack of sensitive outcome measures: The detection of changes in children previously considered to be asymptomatic necessarily requires the use of sensitive and reliable techniques applied by skilled, experienced examiners. Studies that employ group tests or insensitive screening tests to detect deficits are likely to miss existing differences between exposure groups and thus produce falsely negative results.

4. Insufficient control for potentially confounding factors: Many variables associated with increased lead exposure may also compromise neuropsychologic development. The environments in which lead is excessive are generally populated by people of lower socioeconomic status. Accompanying poverty are many factors that adversely influence development. Among these are poor nutrition, increased incidence of infection, poor education, and poor health care. The poor tend to live closer to major highways and to large industries and to eat more canned food—all potential sources of exposure to lead. Also the quality of child rearing and stimulation have been shown to interact with malnutrition (61) and are likely to interact with lead. In a small sample of children, Milar et al (62) have shown that children with elevated blood lead levels tend to have mothers with lower scores than controls on measures of verbal and emotional responsivity and of involvement with their children. Thus, in studies of low-dose lead exposure it is necessary to identify, scale, and control for social and economic factors to avoid confounding. Inadequate attention to confounding variables can lead to false positive conclusions, in which the deleterious effects of poverty or under-nutrition are mistakenly ascribed to lead. On the other hand, powerful socioeconomic factors can swamp the effects of lead, and false negative conclusions may then be drawn.

5. Inadequate sample size: If low doses of lead engender small differences in neurological or psychological functioning, a sample large enough to test the hypothesis of low-dose damage is required. Falsely negative conclusions may be drawn from small studies of low statistical power. Properly speaking, such studies should be described as inconclusive, rather than as negative.

One of the earliest reports of lead and neuropsychological deficit was that of de la Burde & Choate (53). Those authors followed children enrolled in

the Collaborative Perinatal Study (National Institute of Neurological and Communication Disorders and Stroke, i.e. NINCDS) who were reported to have pica and compared their neuropsychologic performance to a group of controls without pica. Blood lead levels were obtained on lead-exposed (LE) subjects but not on controls. Subjects were matched on sex and socioeconomic status. At four years of age, 11 of 69 lead-exposed subjects were rated borderline and 6 were rated defective on the Stanford-Binet IQ test. Of the 71 children in the control group, 7 were rated borderline and none defective. Lead-exposed children had twice the incidence of borderline or abnormal scores as controls on tests of fine motor development and were three times as likely to display abnormal behavior during the testing session. When examined again at age seven years, the LE group had twice the incidence of abnormal neurologic signs, were again significantly inferior in their IQ scores and had eight times the incidence of suspect or abnormal test behavior as compared to controls. Lead-exposed children were reported to display significantly more problems both at home and in school. The authors compared lead levels in shed deciduous teeth from about half the LE and control groups and confirmed that the LE group had higher body burdens of lead. The major strengths of this study are the semiprospective design and the use of shed teeth, which provide a stabler measure than blood of long-term lead exposure. A potential weakness is that children with pica, who in this study comprised the LE group, may a priori be developmentally disturbed or retarded such that their aberrant behavior is a cause rather than a consequence of their elevated lead burden. An additional deficit is that blood lead levels were not measured in the control group. The early lead exposure of the controls was inferred from their place of residence and from the subsequent determination of dentine lead levels in approximately 50% of the group.

Perino & Ernhart (52) compared black preschoolers with blood lead levels between 40 and 70 μg/dl to a control group with blood lead levels below 30 μg/dl. The McCarthy scales of children's ability were administered to both groups. Covariates measured were child's birth weight and birth order, socioeconomic status, number of siblings, parental education, and maternal IQ (Quick Test). Lead level was not related to parental intelligence, socioeconomic status, family size, birth order, or birth weight. Multiple regression analysis with age, parental IQ, and birth weight treated as covariates showed a significant correlation between lead exposure and results on the cognitive scale and on the verbal and perceptual subscales. Lead level was related negatively to parents' education, but this covariate was not entered into the regression model. The authors correlated maternal IQ to child's IQ in both LE and control groups. The correlation coefficient between maternal and child IQ (r) for low-lead groups was 0.52, the degree of correlation usually found in similar comparative studies. For the LE

group, however, r was 0.10, a significantly reduced correlation. The authors suggest that some factor (ostensibly lead) interfered with the usual maternal-child IQ correlation. Although the authors inferred that less educated parents were less able to prevent children from encountering lead, it is possible that lesser education was a significant independent variable with respect to developmental outcome, and may thus have confounded the effects due to lead.

Landrigan et al (51), from the Center for Disease Control, compared 46 lead-exposed children with blood lead levels between 40 and 68 μg/dl to 78 children with blood levels below 40 μg/dl. All children resided near a large primary lead smelter in Texas. LE children had significantly lower scores on the performance IQ (WISC or WPPSI) and lower scores on a finger-tapping test. The groups did not differ in verbal IQ, behavior, or hyperactivity ratings and were closely similar in socioeconomic status, ethnicity, and in duration of residence near the smelter. Criticism of this study has centered on the difference between the mean ages of the LE and control groups (8.3 vs 9.3 years, respectively). The IQ measurements were, however, age-normalized and the finger-tapping scales were regressed for age.

McNeil & Ptasnik (56) compared two groups of children from the same area as that used by Landrigan et al and found no differences in IQ and other neuro-psychological measures. Although LE children differed from controls on the California Test of Personality, the authors attributed that finding to the public attention given them and their condition. Of the 206 children identified as eligible for the study, only 138 (67%) were enrolled. Some of the nonparticipant childrens' families were in litigation against the smelter. This observation raises the possibility that poorly defined selection factors may have contributed to the negative findings obtained. No attempt was made by the authors to examine for possible selection bias.

Lansdown et al (54) studied a group of children living in proximity to a smelter near London. They found a weak inverse relationship between distance of residence from the smelter and blood lead levels. Correlations between blood lead level and intelligence, and reading ability and classroom behavior were not significant. The largest group of the children (138 of 172) with blood lead levels less than 30 μg/dl were, however, resident in a public housing area farthest removed from the smelter and were reported as the most socially disfavored subgroup with the highest incidence of family instability. Children from this group had reported prevalence of hyperactivity of 40%. Social factors in those children with least lead exposure may have confounded or obscured a relationship between lead exposure and outcome. This study illustrates the need for careful handling of potentially confounding social variables in studies of low-dose lead exposure.

David et al (57) called attention to the possible role of lead exposure in

the genesis of the hyperactivity syndrome. David classified 119 children from the pediatric clinic at Downstate Medical Center into five groups: 1. a "pure" hyperactive group with no discernible cause; 2. a group with a "probable" cause; 3. a group with "possible" cause; 4. a lead-poisoned group; and 5. normal controls. Lead levels in groups 1, 3, and 4 were found to be significantly elevated in comparison to controls. Group 1 also excreted more lead in the urine after provocation with a single dose of penicillamine. David et al reported in a later paper (58) that chelation of "pure" hyperactives was associated with improved behavior. These studies are intriguing and important, but should be interpreted cautiously. The authors did not identify or scale any covariates such as socioeconomic status (SES), but relied on the assumption that SES was homogenous in their sample. The improvement in children chelated is intriguing, but the number treated is small and the lack of a placebo control group makes interpretation difficult.

Needleman et al (59) employed shed deciduous teeth as a means of classifying lead exposure. Teeth were collected from 3229 (70%) children attending first and second grade in two towns near Boston. Children were classified as to exposure by virtue of their dentine lead content. High lead and low lead subjects were invited into the study if English was the home language, and if there was no history of prematurity, perinatal complications, lead intoxication, or head injury. Almost all of the children who gave a tooth were rated by the teacher on an eleven-item classroom behavior scale. When included children were compared to excluded, no significant differences in either lead exposure or behavior were found. The children were evaluated on a large panel of neuropsychologic measures, and 39 nonlead covariates were compared. High and low lead subjects were not different on most covariates; no differences in parent attitude scores were found between high and low lead groups. Those factors which differed—maternal IQ and education, maternal age at time of birth, paternal SES and family size—were entered as covariates into an analysis of covariance, with lead as the main effect. High lead children then were found to be significantly inferior to controls on full-scale IQ (WISC-R) on a number of measures of auditory and speech processing, on a test of attention, and on nine of the 11 items of classroom behavior. The teachers' rating of classroom behavior displayed a dose-response effect for all 11 items across all ranges of exposure. The mean blood lead levels in the high tooth lead group was 35 μg/dl four years prior to testing. The major strength of this study is that it deals systematically with each of the five design difficulties described above: a stable measure of lead exposure was employed; comparison of participants with nonparticipants indicated that the influence of ascertainment selection bias on outcome was minimal; a sensitive, well-validated battery of psychological tests was used; careful attention was paid to potentially confounding factors, and any found to differ between the high and low

lead groups were tested systematically for their influence on results; the large sample size gave the study good statistical power. To eliminate the possibility that pica might have been an independent variable in determining outcome, the authors stratified subjects according to pica status; the observed differences in IQ scores and in teacher's rating scales persisted after stratification.

Ratcliffe (60) compared 24 children with blood lead levels above 35 μg/dl (mean = 44.4 μg/dl) to 23 children with blood lead levels equal to or less than 35 μg/dl (mean = 28.2 μg/dl) on the Griffith Developmental Scale, the Frostig Perceptual Quotient, a peg-board test, and a behavioral inventory. The children were classified on the basis of a single blood level taken three years prior to the psychological examination. No statistically significant differences in outcome were found between LE and control groups although controls performed better on the Frostig, on all subscales of the Griffiths, and on the behavior-rating scale. Employing a linear multiple regression model, Ratcliffe found that most of the variance on outcome was attributed to age and attendance at primary school and not to blood lead level. In light of the tendency for low-lead subjects to perform better on all tests, the small sample size, and the possibility that children could have changed their blood lead classification in the three years between blood testing and psychologic examination, these results warrant cautious interpretation.

Baloh and co-workers (55) compared 27 children with at least two blood levels greater than 50 μg/dl to 27 children with blood lead levels greater than 30 μg/dl, matched on age, race, sex, and SES. Children were evaluated on a number of psychological and behavioral outcomes. High-lead subjects were reported by their mothers to be significantly more hyperactive, but no differences in any of the other outcome variables were detected. Control children were chosen from a sample screened for elevated blood lead levels nine months prior to the neuropsychological testing. In the ensuing period, 5 of the 27 controls had increases in blood lead concentration to greater than 30 μg/dl. These changes in blood lead levels raise the possibility that there may have occurred misclassification of subjects.

Evaluation of the Studies

The five design difficulties described above, and probably others not yet recognized, appear to account for most of the differing conclusions drawn by these studies. Epidemiologic evaluations of real world problems, as a result of their inherently observational nature, can never achieve complete control of all salient covariates. No such study can aspire to be without flaw or to yield indisputable etiologic inferences. Assessment of the credibility of epidemiologic analyses must therefore be based on careful evaluation of their design and method, on the internal consistency of their results—

particularly on the issue of whether or not appropriate dose-response relationships are observed—and on the concordance of results with other published data. Those studies outlined here that paid closest heed to methodologic issues [Perino & Ernhart (52), de la Burdé & Choate (53), Landrigan et al (51), and Needleman et al (59)] have found a dose-response association between lead exposure and neuropsychological deficit. Blood lead levels of greater than 40 μg/dl in children under the age of six years appear to be causally associated with increased risk of neuropsychological deficit.

CARCINOGENICITY

Lead has been found in experimental studies in rats, mice, and hamsters to produce renal tumors (63–69). Dosage was by several routes including oral. Levels of exposure in all of the reported studies far exceeded the maximum doses tolerated by man and caused gross morphological damage to the kidney. Positive dose-response relationships were, however, observed between lead dose and tumor incidence, and the interval from onset of exposure to tumor formation was shorter in the more heavily exposed animals (68). In addition to renal tumors, cerebral gliomas have been noted in rats exposed to dietary lead (70).

In an early epidemiological study Dingwall-Fordyce & Lane (71) noted an excess proportionate mortality ratio for malignant neoplasms (all sites combined) in battery workers with "slight" lead exposure (25 deaths observed vs 14.2 expected, $p \leq 0.05$), but no excess mortality was noted among workers with "heavy" exposure to lead. No comment was made in that study as to any site-specific occurrence of excess malignancy.

In a more recent cohort mortality study of lead smelter and battery workers, a significant excess of malignancies at all sites combined was found in smelter workers but not in battery workers (72). In both groups mortality from digestive and respiratory cancer was greater than national rates predicted.

From these data it may be concluded that there is strong evidence for the carcinogenicity of lead in experimental animals. However, insufficient observations have been reported in man to enable a definite conclusion to be reached as to whether lead causes human cancer. Further human study with more intense focus on high-risk exposure groups is required.

MUTAGENICITY

Studies of mutagenesis due to lead have not been uniformly positive in bacterial cell systems (e.g. Ames test) (73), possibly because of the toxicity

of lead to such systems. However, lead has been found to induce in vitro neoplastic transformation of Syrian hamster cells (74) and also to enhance the frequency of transformation induced in that cell system by the SA7 virus (75). In addition, lead has been found in vitro to induce infidelity of DNA replication by DNA polymerase (76).

Smelter workers exposed to lead (and probably also to arsenic) were found in a Swedish study to have an increased prevalence of chromosomal aberrations as compared to controls (77). The frequency of aberrations was correlated with blood lead levels. Exposed workers also had significantly higher frequencies than controls of chromatid aberrations and gaps.

The positive results from these in vitro mutagenic and chromosomal studies strengthen the imperative to examine more closely the possible human carcinogenicity of lead.

REPRODUCTIVE EFFECTS

A large body of experimental data indicates that lead in high doses is toxic to reproductive function in both male and female laboratory animals (78). Female Rhesus monkeys dosed with lead have shown ovarian changes consisting of inhibition in follicle growth, failure of ovulation, and increased ovarian connective tissue (79); hens have manifested delayed attainment of sexual maturity and a decrease in the number of eggs laid (80); ewes have shown a decreased rate of lambing and an increased number of spontaneous abortions (81). Male rats administered lead have shown impotence, prostatic hyperplasia, and reduction in testicular weight (82), while male mice have shown decreased fertility (83) and a dose-related increase in the percentage of spermatozoa with abnormal morphology (84). Administration of lead to adult rats of both sexes appears to produce combined toxic effects on reproduction and on the offspring that are greater than those produced by treatment of either sex alone (85).

Numerous anecdotal reports, most from the first half of this century, describe reproductive toxicity in adult workers of both sexes with occupational exposure to lead. The frequency of spontaneous abortion has been reported to be increased over background both in female lead workers (86, 87) and in the wives of lead workers (88). The possibility exists, however, that in the latter studies the lead workers' wives may have been exposed to lead transported home from the workplace on contaminated skin, hair, shoes, and clothing.

A recent study from Romania (89) reported decreased fertility and an increased prevalence of morphologically abnormal sperm in lead-poisoned male lead workers (sample size = 23; mean blood lead level = 74.5 ± 26 μg/dl) as well as in workers with moderately increased lead absorption

(sample size = 42; blood lead = 52.8 ± 21 μg/dl). Those results require additional confirmation.

CONSIDERATIONS FOR THE FUTURE

Prenatal lead exposure deserves particular emphasis as a subject for future study, particularly in prospective studies of well-defined cohorts. The vulnerability of the young organism to lead has been demonstrated in many species. This heightened suspectibility may be due to a number of factors. The blood-brain barrier is more permeable; young organisms during the period of neurogenesis are more susceptible to many perturbations; less bone is available to act as a buffering and storage site. Lead crosses the placenta, and has been found in the cord blood of neonates (90). To evaluate the neurobehavioral effects of prenatal and early postnatal lead exposure, Beattie et al (91) in Glasgow employed a case-control design and compared the lead levels in household drinking water of retardates and normal controls. They found that maternal exposure to high levels of lead in water during pregnancy was associated with a relative risk of at least 1.7 over controls of bearing a retarded child. In another study, the same group (92) compared infant blood lead levels at one week of age in a subsample of retardates and controls. Retarded children had significantly higher mean blood lead concentrations (25.5 μg/dl vs 20.9 μg/dl). The water supply in Glasgow is soft, plumbosolvent, and in many homes stored in leaden tanks on the roofs.

The interrelationships between lead and aging should also be examined. Lead is stored primarily in bone where it is generally assumed to be metabolically inert. Rabinowitz et al (19) have demonstrated that the biologic half-life is 10,000 days. Given, however, that the aging process is associated with bone resorption and with decreased protein and caloric intake, some turnover of bone lead must occur. It is tempting to speculate as to whether some of the cognitive, attentional, and behavioral changes that are assumed to be a part of the aging process are in fact expressions of lead intoxication. Studies of lead balance, metabolic alterations, and cognitive function in the aged are indicated.

"IS EVERYBODY LEAD INTOXICATED?"

In this review, we trace the historical development of current scientific knowledge of lead intoxication. This process has in many respects been a paradigm of the growth of toxicology. Initially lead poisoning was recognized in both adults and children only by the appearance of fulminant, often fatal disease. Later, with the realization that acute clinically evident poison-

ing could be followed by less obvious sequelae (7), it was recognized that lead could produce a dose-related spectrum of physiologic impairment. Neurobehavioral deficits were identified in populations of apparently asymptomatic children with elevated studies in experimental animals (26), as well as by neurochemical (29, 41) and ultrastructural (42) investigations. These latter studies have suggested candidate mechanisms through which the neurotoxic properties of lead may find expression.

In the population studies of lead toxicity summarized here, the referrent or control groups have consisted of individuals considered "unexposed" to lead. Patterson and co-workers have argued vigorously that because of technological activity, virtually no group unexposed to lead exists in the world today (93, 94).

Employing the most meticulous techniques to minimize contamination, Patterson demonstrated that earlier measurements of naturally occurring lead in food were markedly overestimated and that as a result the contribution of technological processes to environmental contamination was overlooked. Patterson contends, for example, that because of these analytic errors a 4000-fold increase in the lead concentration of canned tuna has been ignored (93). Also, Ericson et al (94) studied lead in the skeletons of pretechnological Peruvian mummies and found that the bone lead concentrations in these samples were approximately 1/600th of those found in contemporary Americans and Englishmen. Patterson argues that such drastic increases as these are to be considered evidence of widespread global lead intoxication.

The case for widespread increases in body lead levels due to technological sources is soundly documented. Whether these increased burdens are to be taken as indicators of intoxication remains, however, unestablished, since intoxication entails a disturbance in the healthy adaptation of the host. The experiments necessary to determine whether these generally increased levels of exposure are associated with intoxication, or whether a "no-effect" level exists, have not yet been undertaken. Given the difficulty of finding a suitable control ("no exposure") group, the conduct of a proper experiment will be a formidable, but vital task.

SUMMARY

Lead has been used by man since antiquity. Knowledge of its toxicity at high dose is old and widely acknowledged. Only recently has attention been directed to the question of whether low doses of lead also produce adverse health effects.

There exist many diverse sources of lead for human exposure. Technology has inserted lead into the diet, the air, and the water. For children, the

most important high-dose source remains paint, but airborne lead, particularly from automobile emissions, is an important moderate-level source for many young children, particularly in cities. Many factors alter the vulnerability of the host to lead. Among them are age, sex, and nutritional status. Younger individuals absorb more lead and are more responsive to the same internal dose. Women are more responsive than men. Iron deficiency and protein deficiency enhance susceptibility of the organism to lead.

Lead acts primarily on sulfhydryl-containing enzymes and generally inhibits their biologic activity. Among the most sensitive enzymes is δ-aminolevulinic acid dehydrase, catalyst of a critical step in the heme biosynthetic pathway and in the synthesis of other cytochromes. The activation of vitamin D appears to be inhibited by lead.

The effects of lead are seen in the brain, the kidney, the erythrocyte, the immune system, and in bone. For children, the most sensitive target organ is the brain. Although some studies of children exposed to lead have failed to demonstrate alterations of neuropsychological functioning at low levels of exposure, numerous carefully designed and executed investigations have found that even low-dose absorption of lead causes reproducible and dose-related damage to the development and function of the central nervous system in children. Studies that have failed to observe evidence for neuropsychologic dysfunction at low levels of lead exposure have generally had design or methodologic defects—such as use of inadequate exposure measures, selection biases, use of weak outcome measures, lack of attention to confounding variables, or small sample size—that mitigate the strength of their apparently negative findings. On the basis of critical review of the current literature, it appears well established that blood lead levels above 40 μg/dl in children under the age of six years are causally associated with an increased risk of irreversible neuropsychological deficit (95).

In the experimental animal, lead has carcinogenic properties. Epidemiologic studies in the workplace provide some suggestion that lead may be a human carcinogen, but these studies require further elaboration. Lead has been shown to be mutagenic in in vitro systems. Reports of increased frequency of chromosomal aberrations in workers exposed to lead have been published.

Experimental studies in rodents, primates, and poultry have shown adverse reproductive effects due to lead. Occupational exposure to lead at high dose has had serious reproductive effects; these effects appear to be mediated through damage caused to reproductive function in both male and female workers.

Among the important areas for future scientific investigations are evaluation of the effects on the fetus of lead exposure during pregnancy and—a totally ignored consideration so far—evaluation of the effects of lead on the physical and psychological events that accompany the aging process.

Recent studies employing meticulous techniques indicate that contemporary man has a body burden of lead 100 times greater than that of the ancients. It is not yet clear whether this increase is associated with adverse health effects. The question remains open and requires serious study. In any event, however, the increase reduces greatly any margin of safety that may exist for lead intoxication.

The convergent evidence from epidemiological, behavioral, biochemical, and neurochemical studies argues that the presently accepted no-effect levels for lead deserve continuous scrutiny. It appears likely that the continued application of increasingly powerful test instruments will find evidence for toxic effects of lead at dose levels yet lower than those currently considered safe.

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